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RAS(ON) and Beyond: Clinical Integration and Strategic Sequencing

Announcer:
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Dr. Arbour:
This is CE on ReachMD, and I'm Dr. Kathryn Arbour. Here with me today is Dr. Eileen O'Reilly, and we've covered a lot in other episodes in this series about RAS inhibitors, both in non-small cell lung cancer and pancreas cancer, and now we're discussing integrating and sequencing these new RAS inhibitors and how we're doing so in our clinical practice.

So, Dr. O'Reilly, how are you using these agents, and what do you think the future looks like?

Dr. O'Reilly:
Yes, so thank you so much for this question. So right now, all of our use of RAS inhibitors, bar the G12C 1%, 1.5%, is in clinical trials, but hopefully that's soon to change. And the initial indication we hope will come from the RASolute 302 trial. And just a quick reminder, this is comparing daraxonrasib, the multi-selective RAS(ON) inhibitor, to chemotherapy in previously treated disease setting. So that, we'll hopefully see in 2026. And if that meets the benchmark, then we'll have a new therapy in pancreas cancer.

But very quickly, we want to integrate it into other disease settings, so into the frontline setting where the impact may be greatest. One of the big challenges of these drugs, and we've touched on it in some of our discussions, is the issue of resistance. We know preclinically, that combining chemotherapy with a targeted therapy and these RAS(ON) inhibitors can deepen responses, right, make the responses more durable and can delay resistance. And that's something that resonates from your world in lung cancer and from our world in the GI field and colorectal cancer with the BREAKWATER data. So we think that's going to hold true with RAS and pancreas cancer as well. So I'm kind of envisaging that we'll have chemo RAS combinations for a majority of people in the frontline setting and then a de-escalation strategy, perhaps, to single agent. And maybe for a subset of individuals who are older or have a less good performance status, that maybe we can start with a single-agent targeted therapy in the frontline. So that's probably the next few years and all of this will have to get teased out in the current randomized studies. And these are just some of the questions and the highlights of what's coming in pancreas cancer.

Dr. Arbour:
I think for lung cancer, we're similarly really trying to cement can we beat docetaxel, a second-line therapy, from that aspect, both in terms of response rate but, really crucially, in terms of the durability of response. What does that meaningfully translate into? A progression-free survival difference, which will hopefully translate to an overall survival benefit in patients. And I think we're really paying attention when we think about daraxonrasib in that second-line setting, quality of life indicators are going to be incredibly important for patients as well as the durability of response. We want lung cancer patients not only to have their disease control, we want them to be thriving in their everyday life, and sometimes that means taking a break from chemotherapy and avoiding the time toxicity of infusions and toxicities of chemotherapy.

We also need targeted therapies that are tolerable in that setting. So I think these quality of life outcomes that will be stemming from the RASolve 301 clinical trial will be so incredibly important as we quantify that for patients.

I think it's an incredibly exciting time for lung cancer to envision how will these drugs look in the second-line setting, but is there a role for these agents in the first-line setting? We currently have multiple clinical trials that are ongoing looking at G12C inhibitors in the first-line setting, including sotorasib and adagrasib and other G12C(OFF) inhibitors. Is there a role for G12C(ON) inhibitors in that setting and what that will look like? Certainly, encouraging preliminary data from that aspect.

And will there be a role one day for pan-RAS inhibitors as initial therapy? One important thing that we're looking at is can we combine these agents with immunotherapy, which is really the backbone for treatment in the first-line setting for non-small cell lung cancer. And I think the early clinical trial data is encouraging from that standpoint that these drugs will be able to be combined with immunotherapy, but definitely stay tuned on other clinical trial results in that setting.

Ultimately, we face the same challenges, I think, that you do in pancreas cancer. Is it going to be an allele-specific drug or a pan-RAS drug? What will be the best strategy? And will there be differences in different patient populations that we'll choose? It may not be the same for those patients with G12C versus G12D versus others, but we're learning so much about both resistance patterns and who will benefit from most approach. And it's really, really, truly exciting times from this perspective.

Dr. O'Reilly:
Yeah, thank you so much.

So it's been great, right, chatting today on these RAS(ON) inhibitors. I think our time is up. We could go on, but thank you so much for listening.

Announcer:
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